REMARKS

Claim 17 is amended to correct a minor typographical error and to further clarify the claimed subject matter. New claims 28-37 are added to further define the claimed subject matter of allowed claim 14. Claims 28-37 find support in the specification at page 4, lines 17-22. This amendment does not introduce new matter or raise new issues requiring consideration by the Examiner. The amendment will place the claims in better condition for appeal.

Applicants acknowledge with appreciation the Examiner's indication in the Final Office Action that claims 14 and 16 are allowed. New claims 28-37 depend from claim 14. Claims 1-5, 7, 11-13, 17-18, and 20-27 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Valentini (U.S. Patent No. 5,939,323) in view of Pheulpin (U.S. Patent No. 3,955,719), Langen (U.S. Patent No. 4,784,055), and Phillips (U.S. Patent No. 4,758,233). Claims 6, 15, and 19 remain rejected under 35 U.S.C. § 103 as allegedly obvious over these same references and further in view of Wozney (U.S. Patent No. 6,187,742).

Applicants submit with this response a Second Declaration of Dr. Hyun Kim under 37 C.F.R. § 1.132. This declaration is provided to further clarify the scientific questions raised by the Examiner in response to the evidence presented in Dr. Kim's original declaration.

The Examiner contends that certain deficiencies in the Kim Declaration were noted in the prior Office Action but were not addressed by Applicants' response. More specifically, the Examiner contends that Applicants did not address the Examiner's statements: (1) that he did not agree that liquids do not have porosity, but rather solids

do, and (2) that "the porosity discussed in Valentini is the final product that results from curing the liquid intermediate." (Final Office Action at p. 3.)

Applicants respond to both statements by respectfully pointing out that the patentability of the claims does not depend on what materials (solids, pastes, or liquids) are considered porous or not porous, but whether Valentini teaches or suggests compositions meeting all of the limitations of the claims. The answer to this question—as demonstrated by the detailed scientific analysis of the Valentini reference provided in both of Dr. Kim's declarations—is no. Dr. Kim's second declaration clarifies that the porosity of the final scaffold can only be produced by including high levels of pore formers in the intermediate composition. These pore formers render the intermediate composition both physically and physiologically uninjectable. (Second Kim Declaration ¶¶ 9, 13.) Accordingly, neither the solid final product described in Valentini, nor the so-called "liquid" intermediate, is capable of being injected through the skin of a patient as required by the claims. An unsupported statement by the Examiner that he does not agree with Dr. Kim's Declaration is not sufficient to rebut this testimony.

Dr. Kim demonstrates: (1) that Valentini's final scaffold is a non-injectable solid and (2) that the size and presence of pore formers of the intermediate composition render that composition uninjectable as well. Specifically, Dr. Kim provides the following testimony in his first declaration:

> [t]he liquid intermediate of Valentini is not injectable because it requires a porosity of 60-90% (col. 8, Table I). The amount of pore-former required to achieve this level of porosity is, at minimum, 9-fold greater than the amount of HYAFF® in the composition (col 8, line 32 and Table I). This large amount of pore former poses a significant problem for injectability. . . . The preferred pore former size used by Valentini is 106-600 microns in diameter (col. 8, line 44). Pore formers of this size

> are too large to be injectable. . . . The pore formers of Valentini are present at inflammatory, non-biocompatible, or superphysiological levels in the liquid intermediate composition. Consequently, these pore formers must be leached out of the scaffold prior to implantation. The leaching process causes the precipitation of the water-insoluble HYAFF® into a partially wet solid state scaffold.

(Kim Declaration at ¶¶ 9-12.) Thus, Dr. Kim demonstrates that Valentini only describes two uninjectable compositions: the intermediate phase with uninjectable levels and sizes of pore formers, and the solid uninjectable scaffold phase. In Dr. Kim's second declaration, he confirms the accuracy of these statements, pointing out that the high levels of pore formers will physically prevent the extrusion of the HYAFF or BMPs through a syringe needle and the skin of a patient. (Second Kim Declaration, ¶¶ 10-11.) In addition, Dr. Kim's second declaration details the scientific basis for his conclusion that the levels of pore formers in Valentini are inflammatory, superphysiological, and non-biocompatible.

The Examiner contends that the expert testimony provided in the Kim Declaration was rebutted by the Examiner's opinion that "even a thick paste is injectable given (1) a larger needle, and (2) a means to force the paste through the needle, i.e., the latter is readily accomplished by a device like a caulking gun." (Final Office Action at p. 3.) Applicants respectfully point out that a paste so thick that it can only be forced through a device as large as caulking gun does not meet the limitations of the claims because such a composition could not be injected through the skin of a patient. And more importantly, as noted above, the thick paste or slurry-like intermediate described in Valentini contains deleterious levels of pore formers—rendering the intermediates even more unsuitable for injection. Dr. Kim's second declaration explains in detail that the

pore formers of Valentini are deleterious because they far exceed physiological concentrations and are toxic to cells. Once these pore formers are removed, the Valentini intermediate solidifies—and is again, incapable of being injected through the skin of a patient. (Second Kim Declaration at ¶¶ 11-13.)

Finally, the Examiner contends that "prior to drying, Valentini discloses a solution that meets the limitation of the instant claims." (Final Office Action at p. 3.) The Examiner states that these intermediate compositions of Valentini contain HYAFFs, pore-formers, tricalcium phosphate, BMPs, and organic solvents and that "[t]here is no indication that the solutions are not injectable, just that it is preferred to [sic] dry the solutions to form an implantable porous scaffold." (Final Office Action at p. 4.) Applicants respectfully disagree for the reasons noted above.

Dr. Kim's testimony – based on his personal experience with the Valentini compositions and technology—is that the compositions described in Valentini are *not* injectable. Specifically, Dr. Kim testifies that the intermediate compositions containing pore formers are pharmaceutically unacceptable and that the removal of pore formers from the Valentini intermediate results in precipitation of the water-insoluble HYAFF into a "partially wet *solid state* scaffold," which is not injectable. (Kim Declaration at ¶ 13, emphasis added.) Thus, even without drying, the Valentini scaffold is not suitable for injection through the skin of a patient.

Moreover, the proper inquiry here is not whether Valentini *can* be modified to achieve a result falling within the claims, but whether or not Valentini, alone or in combination with the other cited references, teaches or suggests modification of the Valentini compositions to achieve the claimed invention. (Manual of Patent Examining

Procedure, Section 2143.01.) The Examiner urges that Valentini teaches "the size and quanitity of NaCl used determines the porosity, pore distribution, and interconnectivity of the final scaffold" and "the porous scaffolds of the invention can be fabricated to any size or shape and can be produced to virtually any desired predetermined pore size depending on the application." (Final Office Action at p. 3.) However, there is no suggestion in Valentini, alone or in combination with the other cited references, to reduce the size and quantity of pore formers in the intermediate to such an extent that this intermediate would be capable of and/or suitable for injection though the skin.

In fact, Valentini teaches away from such a suggestion by stressing the importance of pore formers to create a final scaffold product having at least 60-90% porosity. In view of this emphasis, there would be no motivation by one of skill in the art to eliminate or radically reduce the amount of pore formers recommended by Valentini. Moreover, because Valentini never intends for the intermediate composition to be administered to a patient, the reference provides no information about what levels and sizes of pore formers would be physiologically acceptable for injection into the skin of a patient. As noted by Dr. Kim, the levels of pore formers described in Valentini render the intermediates physiologically deleterious and unsuitable for administration to a patient. (Kim Declaration at ¶ 12; Second Kim Declaration at ¶ 12) And removal of the pore formers from the intermediate results in a "partially wet *solid* state scaffold"—not, as the Examiner asserts—an injectable liquid. (Kim Declaration at ¶ 12, emphasis added).

In summary, Valentini does not teach or suggest compositions that can be injected through the skin of a patient, even when combined with the other cited

references. None of the cited documents suggest any modification to the Valentini compositions that would render them injectable. Accordingly, the combination of Valentini, Pheulpin, Langen, and Phillips does not teach or suggest all the limitations of the claims and does not render claims 1-5, 7, 11-13, 17-18, and 20-27 obvious under 35 U.S.C. § 103.

In rejecting claims 6, 15, and 19 over the combination of the Valentini, Pheulpin, Langen, Phillips, and the additional Wozney reference, the Examiner contends that Wozney teaches the general use of hyaluronic acids and the injection of BMPs. As Applicants have mentioned in previous responses, Wozney does not teach or suggest injectable hyaluronic acid esters, which are recited by the current claims. The Examiner contends that Wozney teaches that BMPs may be delivered by injection. However, this passage in Wozney refers to BMPs in buffers, not in hyaluronic acid ester carriers. The Examiner does not demonstrate how the discussion of injectable administration of BMPs in buffers in Wozney would teach one of skill in the art how to modify the hyaluronic acid ester compositions of Valentini to render them injectable.

The specification and Dr. Kim's declarations clearly demonstrate the novelty and nonobviousness of the claimed compositions comprising BMPs and injectable hyaluronic acid esters over Valentini. Wozney provides no additional suggestion to render the compositions of Valentini injectable and thus, the cited references fail to teach or suggest all of the elements of the claims. Accordingly, the combination of Wozney with Pheulpin, Langen, Phillips, and Valentini does not render claims 6, 15, and 19 obvious under 35 U.S.C. § 103.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 1-7, 11-13, 15, and 17-34 in condition for allowance. Applicants further request the Examiner's reconsideration of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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